RESEARCH ARTICLE

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Ultrasound-Guided Fine-Needle Aspiration Biopsy Of Thyroid Nodules Smaller Than 10 mm in the Maximum Diameter: The Efficacy and Its Correlation with TIRADS Classification

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Abstract

Objective: This retrospective study evaluated the effectiveness of ultrasound-guided fine-needle aspiration cytology (US-FNAc) for diagnosing thyroid nodules less than 10mm and explored the correlation between the TIRADS classification and US-FNAc reports. **Methods:** This analysis of 344 patients with 407 thyroid nodules less than 10mm was conducted from June 2022 to July 2023 at the Centre of Endocrinology and Diabetes, Danang Family hospital, Danang, Vietnam. US-FNAc was performed on all nodules, and cytology was reported according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of US-FNAc were calculated. Correlation between cytology and TIRADS classification was assessed using Spearman's correlation. **Results:** Adequate specimens were obtained in 81% of thyroid nodules after the first FNAc. Cytological diagnoses included 36.6% benign, 12.8% suspicious for malignancy, 1.2% malignant, and 19.7% indeterminate. Among surgically resected thyroid nodules, 78.6% were malignant. US-FNAc demonstrated moderate sensitivity (80%) and high PPV (92.3%) but lower specificity (75%) and NPV (50%) for malignancy in nodules less than 10mm in max diameter. A significant positive correlation ($r = 0.24$, $p < 0.001$) was observed between TIRADS classification and TBSRTC. **Conclusion:** US-FNAc offers moderate sensitivity and high PPV for diagnosing malignancy in smaller than 10 mm thyroid nodules, but specificity and NPV are lower. A positive correlation exists between TIRADS classification and cytological outcomes.

Keywords: Ultrasound-guided fine-needle aspiration cytology- thyroid nodules- TIRADS classification

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Introduction

Thyroid nodules are the second most prevalent endocrine disorder following diabetes, with their prevalence varying considerably based on the detection method, primarily high-frequency ultrasound, which can identify them in 20% to 76% of adults [1, 2]. Ultrasonography (US) based on Thyroid Imaging Reporting and Data Systems (TIRADS) classification and fine needle aspiration cytology (FNAc) have gained widespread popularity for assessing the risk of thyroid nodules for malignancy [3, 4]. According the American Thyroid Association (ATA) guidelines, ultrasound-guided fine-needle aspiration cytology (US-FNAc) is advised for thyroid nodules larger than 10 mm exhibiting intermediate to high suspicion US patterns [5]. Conversely, for patients with nodules measuring 10 mm or less showing suspicious US patterns, active sonographic surveillance is recommended [5, 6]. However, minimally invasive techniques of treatment for both benign and malignant thyroid nodules have been emerging rapidly in recent years [7-9]. In recent guidelines, Minimally invasive techniques (MIT) such as laser ablation (LA), radiofrequency ablation (RFA), microwave ablation (MWA) as well as surgery and active surveillance were recommended for papillary thyroid microcarcinoma (PTMC) treatment [6, 10].

Determining the nature of the small thyroid nodules is a cornerstone before deciding on these treatment methods. And FNAc plays a crucial role in the diagnosis of PTMC [11]. It is a sensitive and specific method for evaluating thyroid lesions and studies have shown that FNAc, in combination with ultrasound, offers a diagnostic accuracy

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of 75-97.5% for early detection of thyroid cancer [12]. It is a rapid, cost-effective, and minimally invasive procedure that allows for the early diagnosis of nature of thyroid nodules [13].

In Vietnam, RFA has been utilized for both benign thyroid nodules and PTMC [14, 15]. Nevertheless, to the best of our knowledge, no investigation has been conducted regarding the effectiveness of FNAc for thyroid nodules measuring less than 10 mm in maximum diameter. This study aims to evaluate the accuracy of US-FNAc for diagnosing thyroid nodules smaller than 10mm and investigate the relationship between TIRADS classification and US-FNAc results.

Materials and Methods

Study design and patient's selection

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Institutional Review Board of Danang Family hospital, Danang, Vietnam (No.: 012/QĐ-NCKH/FAMILY), and written informed consent for FNAc's procedures was obtained for all patients.

We reviewed computerized medical records (Ehealth program) of 914 patients who underwent thyroid US and thyroid US-FNAc from June 2022 through July 2023 at the Centre of Endocrinology and Diabetes, Danang Family hospital, Danang, Vietnam. 390 patients who presented with thyroid nodules with less than 10mm in maximum diameter were extracted from the Ehealth program. Among them, 46 patients lacked the thyroid US or function test results in the Ehealth program. Finally, 344 patients with 407 nodules were involved in this study.

All patients experienced thyroid US-FNAc procedure have been collected in this current study because they satisfied the following criteria: (1) nodules with a maximum diameter less than 10 mm; (2) thyroid US performed with ACR-TIRADS classification; (3) thyroid function tests including serum free thyroxine (FT4) and thyroid-stimulating hormone (TSH) concentrations were collected; and (4) thyroid cytology reported according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). We provided detailed information about the FNAc procedure to each patient before they underwent the procedure.

Thyroid US examination

All patients underwent thyroid US performed by radiologists with over 3 years of experience at the Department of Diagnostic Imaging in the same hospital, using an 8-12 MHz linear probe on a real-time ultrasound machine (Acuson NX2 or NX3, Siemens Medical Solutions, California, USA). The reasons for performing thyroid ultrasound included: 1) incidentally identified palpable neck mass; 2) a known history of thyroid nodules with regular follow-up; and 3) routine health check-up. Thyroid ultrasound findings were recorded in the Ehealth program, and all thyroid nodules were categorized according to the ACR-TIRADS system based on five sonographic features (Figure 1 A-B): composition, echogenicity, shape, margin, and echogenic foci. The three diameters of each nodule were measured [3, 4].

Thyroid US-FNAc procedure

FNA procedure was performed in an outpatient setting with patients in the supine position and mild neck extension under ultrasound guidance by a single, licensed endocrinologist with over 5 years of experience (Van Bang Nguyen). Doppler mode was used to visualize and avoid vascular structures during needle insertion, minimizing the risk of injury.

An ultrasound transducer covered with a thin layer of sterile, water-soluble gel was placed on the neck. Under continuous ultrasound guidance, the suspected nodule was punctured using a parallel approach with a 25-gauge, 1-inch needle attached to a 5 or 10 ml syringe. No local anesthesia was used. Once the needle reached the nodule, it was gently moved back and forth within the nodule in a fan-like motion about ten times under negative pressure to aspirate a sample. After removal of the needle, negative pressure was released, and the aspirated specimen was spread onto a slide and air-dried. This slide was then fixed in 95% alcohol and sent to the pathology laboratory for evaluation after Giemsa staining.

Pathological dianogsis

Cytological diagnoses were performed at the pathology laboratory by two pathologists with more than 5 years of experience. Cytological results were reported following The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [16]: (I) nondiagnostic or unsatisfactory; (II) benign; (III) atypia of undetermined significance or follicular lesion of undetermined significance; (IV) follicular neoplasm or suspicious for a follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant (Figure 2 A-B).

Patients with TBSRTC categories IV, V, and VI were offered surgery or radiofrequency ablation for PTMC based on their individual preferences and signed informed consent. If surgery, the histological diagnoses were reported according to the World Health Organization (WHO) histological classification of thyroid tumors (Figure 3 A-B) [17].

Statistical analyses

SPSS version 20.0 for Windows was used in this study for all statistical analyses. Demographic information of patient characteristics (age, gender), thyroid US features (nodule position, largest nodule diameter), and blood test (FT4, TSH) were described by calculating means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were given as percentages. Correlation between cytological results and ultrasonographic characteristics (ACR-TIRDS classification) of individual nodules was performed with Spearman correlation. Agreement between cytological and histopathological findings was used to assess the diagnostic accuracy of US-FNAc. US-FNAc was deemed accurate when the two results aligned, and conversely. A p-value <0.05 was considered statistically significant.

Results

From June 2022 through July 2023, we identified 344 patients with 407 nodules meeting the inclusion criteria via the Ehealth program. The diagnostic performance of US-FNAc was calculated in 28 patients who underwent surgery and had histopathological confirmation. We classified thyroid nodules with a cytological result of "benign" as negative for malignancy, while those with "suspicious for malignancy" or "malignant" cytology were classified as positive for malignancy, as per our study protocol. Nodules with "indeterminate" and "inadequate" cytology after the initial US-FNAc were excluded from calculating sensitivity, specificity, accuracy, negative predictive value, and positive predictive value.

Table 1 showed the general informations of 344 patients with 407 thyroid nodules with a maximum diameter less than or equal to 10 mm, including information on age, sex, nodule location, size, FT4, and TSH levels. The mean age of the patients was 46.2 years, and 71.8% were female. Most nodules were located on the right thyroid lobe (53.6%), and the average diameter was 6.74 mm with 83.5% greater than 5mm in maximum diameter. The mean FT4 level was 1.63 ng/dL, and the mean TSH level was 1.31 mIU/ml.

Table 2 and Table 3 evaluated the diagnostic yield and cytological characteristics of thyroid nodules using US-FNAc. The incidence of adequate specimens was 287 (81%) nodules after the first FNAc procedure. Among the diagnosed nodules, 36.6% (149 lesions) were classified as benign, 12.8% (52 lesions) were suspicious for malignancy, 1.2% (5 lesions) were malignant, and 19.7% (80 lesions) were indeterminate according to the TBSRTC classification system. Furthermore, thyroid surgery was performed on 28 patients with a total of 28 thyroid nodules. Notably, 22 of these nodules (78.6%) were confirmed to be malignant. Furthermore, for nodules less than 10 mm in diameter, US-FNAc demonstrated moderate sensitivity (80%) and high positive predictive value (92.3%) for malignancy, but lower specificity (75%) and negative

Table 1. The Demographic Information of Patients with Thyroid Nodules with a Maximum Diameter of Less than 10 mm

Characteristics	Summary statistics
Number of patients	344
Number of nodules	407
Age (years) [(mean ± SD) (range)]	46.2 ± 12.7 (24 - 85)
Female [n (%)]	247 (71.8)
Nodule position [n (%)]	
Left	160 (39.3)
Isthmus	29 (7.1)
Right	218 (53.6)
Mean largest nodule diameter (mm) [(mean ± SD) (range)]	6.74 ± 1.92 (2 - 10)
< 5mm (n,%)	67 (16.5)
>=5mm (n,%)	340 (83.5)
FT4 (ng/dL) [(mean ± SD) (range)]	1.63 ± 1.03 (0.005 - 6.8)
TSH (mIU/ml) [(mean ± SD) (range)]	1.31 ± 0.36 (0.31 - 4.1)

SD, Standard deviation; FT4, Free Thyroxine; TSH, Thyrotropin

Table 2. Agreement between Cytological and Histopathological Findings

Cytology	Lesion number in cytology (n,%)	Operated lesion number (n,%)	Malignant number (n, %)
Benign	149 (36.6)	6 (4.02)	3 (2.01)
Suspicious for malignancy	52 (12.8)	8 (15.4)	7 (13.5)
Malignant	5 (1.2)	5 (100)	5 (100)
Indeterminate	80 (19.7)	8 (10.0)	6 (7.5)
Inadequate	121 (29.7)	1 (0.83)	1 (0.83)

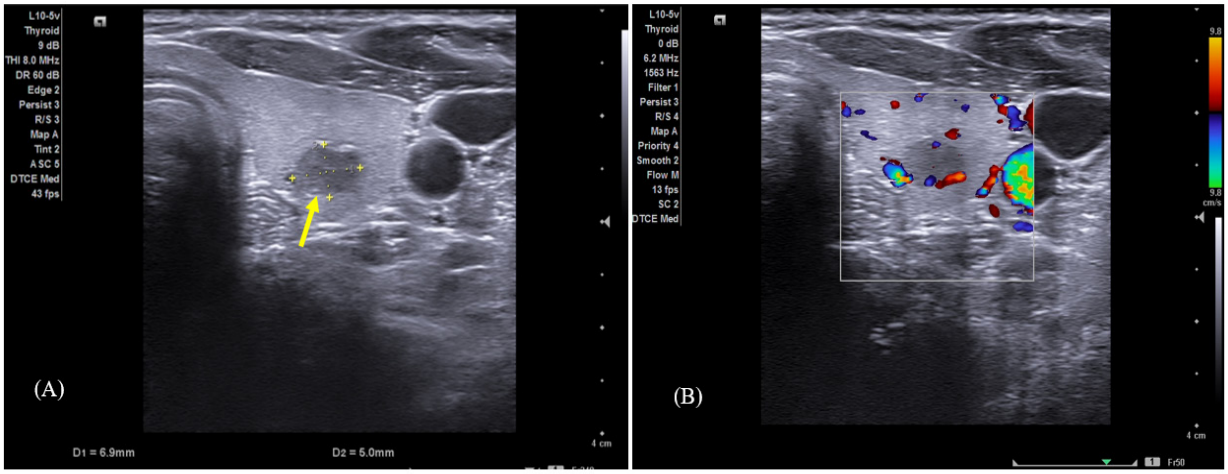

Figure 1. A 29-Year-Old Woman Visited Our Center because of an Incidental Thyroid Nodule. In thyroid ultrasonography: A hypoechoic nodule of 6.9 mm in the max diameter in the left thyroid lobe with microcalcification (yellow arrow) (A) and without flow Doppler (B). ACR-TIRADS 2017: V.

Table 3. The Diagnostic Accuracy of US-FNAc

	Malignant number	Benign number	Total
Malignant number	12	45	57
Benign number	3	146	149
Total	15	191	
Sensitivity = 80%; Specificity = 75%; Accuracy = 78.9%; PPV = 92.3%; NPV = 50.0%			

PPV, Positive predictive value; NPV, Negative predictive value

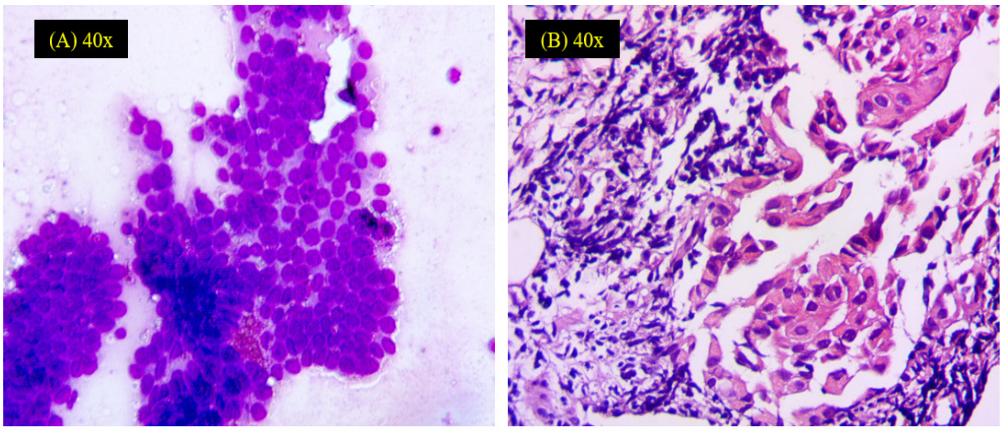

Figure 2. FNA (A) and CNB (B) Confirmed: papillary thyroid carcinoma (Classification VI Bethesda).

predictive value (50%).

A statistically significant positive correlation ($r = 0.24$, $p < 0.001$) was observed between the TIRADS classification and Bethesda criteria using Spearman's analysis (Table 4). This indicates that as the number of suspicious features in a nodule increases according to the TIRADS system, the likelihood of malignancy also rises in line with the Bethesda criteria. This finding suggests that combining US-FNAc with TIRADS classification can potentially improve diagnostic accuracy of subcentimeter thyroid nodules.

Discussion

As reported in literature, TNs are prevalent and their detection is on the rise in clinical practice [18]. In which

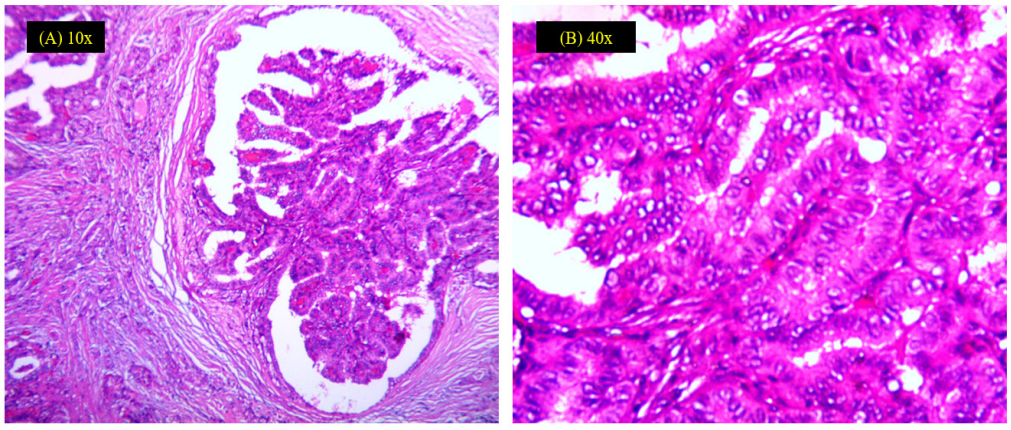

Figure 3. (A) and (B) the Histological Diagnoses Reported: papillary thyroid carcinoma

Table 4. Correlation between Thyroid Cytological Results and Thyroid Ultrasonographic Characteristics

TIRADS	Bethesda						Total (n,%)	r (p)
	1 (n,%)	2 (n,%)	3 (n,%)	4 (n,%)	5 (n,%)	6 (n,%)		
2	6 (5)	9 (6)	0	0 (0)	0	0	15	0.24 (< 0.001)
3	25 (20.8)	23 (15.4)	2 (7.7)	5 (9.3)	2 (3.8)	1 (20)	58	
4	75 (62.5)	92 (61.7)	14 (53.8)	38 (70.4)	34 (65.4)	0	253	
5	14 (11.7)	25 (16.8)	10 (38.5)	11 (20.4)	16 (30.8)	4 (80)	80	

thyroid nodules less than 10mm is significant, ranging from 50% to 77.4% according to various studies [19, 20]. As defined by the WHO classification system, PTCs measuring less than 10 millimeters in diameter are categorized as PTMC [21]. The incidence of PTMC is on the rise globally, posing a significant challenge. Specifically, the percentage of PTMC rose from 6.1% in 1962 to approximately 9% in 1990, further increasing to 54% in 2005, before settling at 43.1% in 2009 [22]. Despite the slow-growing nature of PTC, debate persists regarding the clinical benefit of early diagnosis via US-FNAc. Both the European Thyroid Association (ETA) 2023 and the ATA 2015 recommend delaying FNAc for nodules less than 1 centimeter in size until treatment becomes necessary, assuming immediate intervention is not required [5, 6]. However, US-guided thermal ablation such as RFA, LA and MWA has been emerging as one of the treatment options of PTMC patients who wish for a minimally invasive management approach beside AS and surgery.

Accurately characterizing the nature of small thyroid nodules through diagnostic tests is paramount for guiding treatment decisions. And FNAc plays as an important method for evaluating thyroid lesions with a sensitivity of 89.31%, specificity of 48.44%, PPV of 78%, NPV of 68.89%, and accuracy of 75.89% [23]. In addition, this technique is a rapid, cost-effective, and minimally invasive procedure that allows for the early diagnosis of nature of thyroid nodules [24].

In our study, US-FNAc for subcentimeter thyroid nodules demonstrated moderate sensitivity (80%) and high positive predictive value (92.3%) for malignancy, but lower specificity (75%) and negative predictive value (50%). However, the incidence of inadequate specimens was 29.7% nodules after the first FNAc procedure. These results are in line with previous studies with the results of previous studies that reported values ranging from 10.5 to 31% [25, 26, 27]. Moon et al showed the inadequate specimens rate in US-FNAc procedure for subcentimeter thyroid nodules was about 17.8% and sensitivity, specificity value of US-FNAc were 91.6, 98.5, respectively [28]. And, smaller thyroid nodules were associated with higher rates of inconclusive US-FNAc samples and false-positive ultrasound findings [28]. A similar malignancy rate of around 13.7% observed in both ≤5mm and >5mm nodules based on cytological diagnosis from the Mendes study suggests potential value in using US-FNAc for clinical decision-making regarding early imaging evaluation or intervention for specific patient groups [29].

Also, in this study, the TIRADS classification and TBSRTC observed a statistically significant positive correlation. Our findings align with Mendes et al study [29] regarding malignancy rates in TIRADS 2 is 0.91% ; TIRADS 3, 2.87% ; TIRADS 4A, 12.26% ; TIRADS 4B, 34.43% ; TIRADS 4C, 66.6% and TIRADS 5, 85.7%. Noticeably, these author proved TIRADS and Bethesda criteria were positively correlated.

How TIRADs and US-FNAc will shape the future of small thyroid cancer diagnosis, AI-powered TIRADS classification has emerged as a transformative tool in the diagnosis of small thyroid nodules, revolutionizing the US-FNAc procedure. By leveraging AI's superior image analysis capabilities, precise target selection, and risk stratification, TIRADS classification minimizes unnecessary FNAs, enhances diagnostic accuracy, and optimizes the FNA workflow, ultimately improving patient outcomes. AI integration into TIRADS-FNAc holds immense promise for the future of thyroid cancer diagnosis, particularly for small nodules [21].

Several limitations inherent to this study warrant consideration. First, the retrospective nature of the design introduces the possibility of selection bias, particularly due to the exclusion of inadequate and indeterminate initial cytology results for sensitivity and specificity analysis of US-FNAc as well as small sample size. Second, while RFA offers certain advantages, its preference over surgery in patients with Bethesda IV/V thyroid nodules significantly reduces the available sample size for assessing the sensitivity and specificity of diagnostic tests. Third, the six radiologists and two pathologists in this study could lead to inconsistencies in the interpretation of ultrasound examinations as well as cytological diagnoses. This potential variability should be considered when evaluating the results. Last but not least, recognizing the potential limitations associated with our knowledge base, we restricted this study's review to existing cytological reports without independent examination of the original slides. This approach may not account for nuances observable on the slides themselves.

In conclusion, our findings underscore the effectiveness of US-FNAc in diagnosing subcentimeter thyroid nodules, before deciding suitable treatment therapy. The positive correlation between TIRADS and TBSRTC strengthens the role of both systems in guiding clinical management and optimizing patient outcomes, particularly for this challenging subset of thyroid nodules.

List of Abbreviations

AS: Active Surveillance
ATA: American Thyroid Association
ETA: European Thyroid Association
FNAc: Fine Needle Aspiration Cytology
FT4: Free Thyroxine
LA: Laser ablation
MWA: Microwave ablation
MIT: Minimally invasive techniques
NPV: Negative predictive value
PTMC: Papillary thyroid microcarcinoma
PPV: Positive predictive value
RF: Radiofrequency
RFA: Radiofrequency ablation
SD: Standard deviation
TIRADS: Thyroid Imaging Reporting and Data Systems
TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology
TSH: Thyrotropin
US-FNAc: Ultrasound-Guided Fine-Needle Aspiration Cytology
US: Ultrasound
WHO: World Health Organization

Author Contribution Statement

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Acknowledgements

Declarations

Ethics statement

Ethics approved by the Ethics Committee of the Institutional Review Board of Danang Family hospital, Danang, Vietnam (No.: 012/QĐ-NCKH/FAMILY), and written informed consent for FNAc's procedures was obtained for all patients following.

Availability of data and materials

Availability of data and materials supporting our findings will be shared upon request.

Competing interests

Conflict of interest relevant to this article was not reported.

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